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Renal Sympathetic Denervation Reduces Left Ventricular Hypertrophy and Improves Cardiac Function in Patients With Resistant Hypertension

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Objectives This study investigated the effect of catheter-based renal sympathetic denervation (RD) on left ventricular hypertrophy (LVH) and systolic and diastolic function in patients with resistant hypertension.

Background LVH and diastolic dysfunction are associated with elevated sympathetic activity and increased morbidity and mortality. The effect of RD on LVH and LV function is unclear.

Methods Forty-six patients underwent bilateral RD, and 18 patients served as controls. Transthoracic echocardiography was performed at baseline, and after 1 month and 6 months.

Results Besides reduction of systolic and diastolic blood pressure (−22.5/−7.2 mm Hg at 1 month and −27.8/−8.8 mm Hg at 6 months, $p < 0.001$ at each time point), RD significantly reduced mean interventricular septum thickness from 14.1 ± 1.9 mm to 13.4 ± 2.1 mm and 12.5 ± 1.4 mm ($p = 0.007$), and LV mass index from 53.9 ± 15.6 g/m$^{2.7}$ (112.4 ± 33.9 g/m^2) to 47.0 ± 14.2 g/m$^{2.7}$ (103.6 ± 30.5 g/m^2) and 44.7 ± 14.9 g/m$^{2.7}$ (94.9 ± 29.8 g/m^2) ($p < 0.001$) at 1 month and 6 months, respectively. The mitral valve lateral E/E′ decreased after RD from 9.9 ± 4.0 to 7.9 ± 2.2 at 1 month and 7.4 ± 2.7 at 6 months ($p < 0.001$), indicating reduction of LV filling pressures. Isovolumic relaxation time shortened (baseline 109.1 ± 21.7 ms vs. 85.6 ± 24.4 ms at 6 months, $p = 0.006$), whereas ejection fraction significantly increased after RD (baseline: 63.1 ± 8.1% vs. 70.1 ± 11.5% at 6 months, $p < 0.001$). No significant changes were obtained in control patients.

Conclusions Besides the known effect on blood pressure, our study showed for the first time that RD significantly reduces LV mass and improves diastolic function, which might have important prognostic implications in patients with resistant hypertension at high cardiovascular risk. (J Am Coll Cardiol 2012;59:901–9) © 2012 by the American College of Cardiology Foundation

Hypertension is a risk factor for coronary artery disease, myocardial infarction, and stroke. Patients with therapy-refractory hypertension are at particular risk for cardiovascular events. Even before clinical events occur, hypertension induces changes of the heart, including left ventricular hypertrophy (LVH) and cardiac fibrosis (1). These structural alterations are associated with functional impairment of the left ventricle (LV), i.e., abnormal diastolic relaxation and increased diastolic filling pressures. Notably, diastolic dysfunction may already be present in hypertensive patients with normal LV mass (2,3).

See page 910

LVH and diastolic dysfunction have been linked to cardiovascular morbidity and mortality (4,5). Regression of LVH was shown to improve cardiovascular outcome independently of other risk factors, and thus has been suggested as an intermediate endpoint (6,7). However, despite a similar reduction of blood pressure (BP), efficacy on LVH regression varies among different antihypertensive drugs (8).

The cause of resistant arterial hypertension is multifactorial. Chronic activation of the sympathetic nervous system plays a central role in the pathophysiology of both BP elevation and development of LVH (9–11). Reduction of renal sympathetic afferent and efferent activity by percuta-

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Abbreviations and Acronyms

BMI = body mass index
BP = blood pressure
DBP = diastolic blood pressure
IVSTd = end-diastolic interventricular septum thickness
LA = left atrium
LV = left ventricle
LVH = left ventricular hypertrophy
RD = renal sympathetic denervation
RWT = relative wall thickness
SBP = systolic blood pressure

neous, catheter-based endovascular radiofrequency ablation of the renal sympathetic nerves effectively decreased systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with resistant hypertension (12,13). However, the impact of renal sympathetic denervation (RD) on LVH is unclear. Therefore, we evaluated whether this new therapeutic approach has a positive effect on LVH as measured by hypertensive end-organ damage and on diastolic dysfunction.

Methods

The study was approved by the local ethics committees in accordance with the Declaration of Helsinki. Patients were treated between October 2009 and January 2011, with subsequent follow-up for 6 months. All patients provided written informed consent.

Study subjects. Eligible patients were older than 18 years and had an office BP of ≥160 mm Hg (≥150 mm Hg for type 2 diabetes patients) or more, despite treatment with at least 3 antihypertensive drugs (including a diuretic), with no changes in medication for a minimum of 3 months before enrollment. To exclude white coat hypertension, 24-h BP recordings and home BP protocols were consulted in addition to office BP measurements at the hospital before enrollment. Patients with secondary causes of hypertension were excluded. Further exclusion criteria have been reported previously (13,14). Forty-six patients underwent renal denervation, and 18 patients were in the control group. In all patients, the same inclusion/exclusion criteria were applied as part or extension of the randomized controlled Symplicity HTN-2 (Renal Denervation in Patients With Uncontrolled Hypertension) protocol (NCT00888433) (13).

BP measurements. Before BP measurements, the adherence of the patients to their antihypertensive medications was ensured. BP and heart rate were recorded after 10 min of supine rest using an automatic oscillometric monitor (Omron HEM-705, Omron Healthcare, Vernon Hills, Illinois) on the brachial artery. BP was measured on the same side throughout the study. Averages of triplicate measurements with 1-min intervals were used for analysis.

Transthoracic echocardiography. Transthoracic echocardiography was performed at baseline, 1-month, and 6-month follow-up using a Philips iE 33 ultrasound system (Amsterdam, the Netherlands) equipped with a multifrequency transducer and tissue Doppler imaging software according to the Guidelines of the American Society of Echocardiography (15). Data were analyzed and interpreted by 2 experienced echocardiographers blinded to treatment status and sequence of the images.

Diastolic functional parameters were recorded following recent recommendations of the American Society of Echocardiography (16). The LV mass was calculated from LV linear dimensions using the Devereux formula (15,17). LV mass was indexed to the body surface area and to the height to the 2.7 power (15,18), as indicated. LVH was considered present when the LV mass exceeded 115 g/m^2 and 48 g/m$^{2.7}$, respectively, for men and 95 g/m^2 and 44 g/m$^{2.7}$, respectively, for women (15). Relative wall thickness (RWT) was calculated by end-diastolic interventricular septum thickness (IVSTd) + end-diastolic posterior wall thickness/end-diastolic internal dimension, with RWT >0.42, indicating concentric LV remodeling/hypertrophy (15,19).

RD procedure. Renal angiograms were performed via femoral access to confirm anatomic eligibility. In the same session, RD was performed using the Symplicity or Flex catheter (by Ardian, Palo Alto, California), as previously reported (14). Up to 6 ablations at 8 W for 2 min each were performed in both renal arteries.

Statistical analysis. Data are presented as mean ± SD. Differences in the mean values were compared using a 2-tailed *t* test for continuous variables and Fisher-Yates testing for nominal variables. Changes of all parameters with multiple measurements, including p for statistical trend, were analyzed from baseline to 1 and 6 months by 2-factor analysis of variance for repeated measurements. The Scheffé correction algorithm was used to compute post hoc comparisons of significant values. A comparison between linear trends in treatment and control groups was performed using the group square linear trend interaction test. For N-terminal pro–B-type natriuretic peptide values with a highly skewed distribution, statistical significance was calculated using the Wilcoxon-Mann-Whitney test. A p value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS statistical software (version 12.0, SPSS Inc., Chicago, Illinois).

Results

Patient characteristics. Sixty-four patients with arterial hypertension refractory to medical therapy were included in the study. Forty-six patients were treated with RD, 18 patients served as controls. The mean age in the treatment group was 63 ± 10.1 years; males were a majority of 67% (Table 1). The mean body mass index (BMI) was above normal with 28.6 ± 3.3 kg/m^2, and 27.4% of patients had a BMI >30 kg/m^2. On average, patients were taking 4.7 different antihypertensive drugs. The most frequently used substance groups were beta-blockers (98%), ACE inhibitors or AT1-receptor blockers (98%), and calcium channel blockers (87%). All patients were on diuretic agents. The patient demographic and clinical characteristics did not differ between the RD and control groups (Table 1).

BP control by RD. At baseline, the mean sitting office SBP/DBP in the treatment group (180.7 ± 18.3/95.8 ±

Table 1 Patient Characteristics at Baseline

	Renal Denervation (n = 46)	Control (n = 18)	p Value
Age, yrs	63.1 ± 10.2	63.0 ± 15.3	0.977
Male	31 (67%)	11 (61%)	0.771
BMI, kg/m^2	28.6 ± 3.4	28.1 ± 3.8	0.595
Coronary artery disease	20 (44%)	7 (39%)	0.785
Atrial fibrillation	7 (15%)	2 (11%)	1.000
Stroke	8 (17%)	4 (22%)	0.726
Type 2 diabetes	21 (46%)	7 (39%)	0.781
Hypercholesterolaemia	32 (70%)	10 (56%)	0.382
Smoking	14 (30%)	3 (17%)	0.086
Number of antihypertensive drugs	4.7 ± 0.5	4.8 ± 2.5	0.979
Patients receiving (drug class)			
ACE inhibitors/ARBs	45 (98%)	18 (100%)	1.000
Direct renin inhibitors	17 (37%)	5 (28%)	0.770
Beta-blockers	45 (98%)	16 (89%)	0.189
Calcium-channel blockers	40 (87%)	13 (72%)	0.267
Diuretics	46 (100%)	18 (100%)	1.000
Oral sympatholytics	23 (50%)	7 (39%)	0.579

Values are mean ± SD or n (%). Statistical differences between groups, where applicable, are indicated in the far-right column.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index (kg/m^2).

10.1 mm Hg) and the control group (184.5 ± 22.1/98.2 ± 13.6 mm Hg, p = 0.503/0.496) were similar (Table 2, Figs. 1B and 1C). RD significantly reduced BP at 1 month (158.2 ± 17.6/88.6 ± 10.9 mm Hg, p < 0.001/0.001) and 6 months (152.9 ± 22.4/87.0 ± 12.9 mm Hg, p < 0.001/0.014), whereas BP remained unchanged in the control group (Table 2, Fig. 1). In the control group, the number and dosage of antihypertensive drugs remained constant during follow-up. After RD, the number of antihypertensive drugs could be reduced in 7 patients (15%), resulting in an average of 4.5 ± 1.6 antihypertensive drugs at 6 months versus 4.7 ± 1.5 at baseline (p = 0.402). Additionally, in a further 8 patients (17%), the dosage of at least 1 antihypertensive drug was reduced after RD.

Regression of LVH. The LV mass index decreased continuously in the RD group, from 53.9 ± 15.6 g/m$^{2.7}$ (112.4 ± 33.9 g/m^2) at baseline to 47.0 ± 14.2 g/m$^{2.7}$ (103.6 ± 30.5 g/m^2) at 1 month (p < 0.001/0.01) and 44.7 ± 14.9 g/m$^{2.7}$ (94.9 ± 29.8 g/m^2) at 6 months (p < 0.001/0.001 vs. baseline, p for trend <0.001/0.004), respectively, whereas LV mass slightly increased in the control group, from 55.7 ± 15.3 g/m$^{2.7}$ (114.8 ± 41.6 g/m^2) at baseline to 58.6 ± 16.1 g/m$^{2.7}$ (118.7 ± 30.1 g/m^2) at 6 months (p = 0.007/0.009 vs. RD) (Table 2, Fig. 2A). In the RD group, 63% and 33% had LVH (indexed to height$^{2.7}$) at baseline and after 6 months, respectively. Consistently, after RD, but not in control patients, there was a significant reduction of the interventricular septum thickness (RD: 14.1 ± 1.9 mm at baseline vs. 13.4 ± 2.1 mm at 1 month, p = 0.005, vs. 12.5 ± 1.4 mm at 6 months, p = 0.009, p for trend = 0.007) (Fig. 2B).

The effect of RD on LV mass regression correlated with the degree of myocardial hypertrophy at baseline and was most evident in patients with LVH at baseline. Although in patients without LVH (indexed to height$^{2.7}$), no significant change of LV mass after RD occurred, in the subgroup with LVH at baseline (n = 29, 63%), RD markedly reduced LV mass index by −8.0 ± 11.9 g/m$^{2.7}$ (p = 0.08 vs. no LVH, p = 0.06 vs. baseline) and −13.5 ± 10.4 g/m$^{2.7}$ (p = 0.009 vs. no LVH, p = 0.004 vs. baseline) after 1 month and 6 months, respectively (Figs. 2C and 2D). Eccentric LVH, i.e., RWT ≤0.42 was evident in only 2 patients before RD and was not detected 6 months post-intervention. Consistently, LV mass regression by RD was predominantly due to a marked decrease of LV wall thickness, rather than a reduction of end-diastolic LV internal dimension (Table 2). In patients without LVH, 53% and 41% exhibited concentric LV remodeling at baseline and 6 months after RD, respectively.

Improvement of systolic function. The LV end-systolic volume was significantly reduced by RD (32.8 ± 15.6 ml at baseline, to 27.7 ± 12.8 ml at 1 month, p < 0.001, and 25.6 ± 12.5 ml at 6 months, p = 0.001 vs. baseline, p for trend <0.001, p = 0.03 vs. control). This was associated with a significant increase of the LV ejection fraction in the RD group (LV ejection fraction: 63.1 ± 8.1% at baseline to 69.1 ± 7.5% at 1 month, p < 0.001, and 70.1 ± 11.5% at 6 months, p = 0.001, p for trend = 0.001) (Table 2). Conversely, no reduction of LV end-systolic volume and no improvement of LV ejection fraction were obtained in control patients (Table 2).

Improvement of diastolic function. In addition, regression of LV mass in patients who underwent RD was accompanied by an improvement of diastolic functional parameters, whereas in control patients, a trend towards progression of diastolic dysfunction was observed (Table 2). The mitral E-wave deceleration time shortened steadily after RD, from 227.2 ± 66.5 ms at baseline to 211.3 ± 57.6 ms at 1 month and 185.2 ± 67.1 ms at 6 months (p = 0.013 vs. baseline, p for trend = 0.003). Consistent with an improvement of diastolic LV relaxation, RD significantly reduced the isovolumic relaxation time from 109.1 ± 21.7 ms at baseline to 93.0 ± 22.4 ms at 1 month (p < 0.001 vs. baseline) and 85.6 ± 24.4 ms at 6 months (p = 0.006 vs. baseline, p for trend 0.002, p = 0.008 vs. control).

Tissue Doppler imaging revealed a significant increase of the diastolic relaxation velocity of the lateral mitral annulus following RD (Table 2). Furthermore, the ratio of mitral inflow velocity to annular relaxation velocity (lateral E/E′), a marker of LV diastolic filling pressure, significantly decreased as early as 1 month after RD (9.9 ± 4.0 at baseline vs. 7.9 ± 2.2 at 1 month, p < 0.001) and continued to decline throughout the 6-month follow-up (7.4 ± 2.7, p = 0.001 vs. baseline, p for trend <0.001, p < 0.001 vs. control) (Fig. 3A). The percentage of patients with normal LV filling pressures, i.e., an E/E′ ratio ≤8, increased from 39% at baseline to 58% at 1 month and 68% at 6 months post-RD, whereas the percentage of patients with increased LV filling pressures based on the E/E′ ratio (E/E′ ratio

Table 2 Blood Pressure, Echocardiographic, and Laboratory Parameters in RD and Control Patients at Baseline, 1 Month, and 6 Months

	Renal Denervation (n=46)				Control (n=18)				
	Baseline	1 Month	6 Months	p for Trend	Baseline	1 Month	6 Months	p for Trend	RD vs. Control Differential Efficacy
Basic hemodynamic parameters									
Resting SBP (mm Hg)	180.7 ± 18.3	158.2 ± 17.6	152.9 ± 22.4	<0.001	184.5 ± 22.1	181.6 ± 26.3	182.8 ± 24.6	0.864	0.039
Resting DBP (mm Hg)	95.8 ± 10.1	88.6 ± 10,9	87.0 ± 12.9	<0.001	98.2 ± 13.6	98.0 ± 12.7	99.8 ± 16.5	0.792	0.041
Peripheral PP (mm Hg)	84.3 ± 14.9	69.6 ± 13.6	65.2 ± 17.0	<0.001	86.2 ± 19.1	83.6 ± 18.2	83.0 ± 17.0	0.798	0.041
Heart rate at rest (beats/min)	66.5 ± 12.2	61.9 ± 9.5	60.9 ± 16.3	0.003	66.3 ± 16.5	66.4 ± 11.9	64.3 ± 14.0	0.752	0.047
Echocardiographic parameters									
Left atrial diameter (mm)	45.2 ± 6.1	43.0 ± 5.3	42.5 ± 6.0	<0.001	43.7 ± 5.3	44.5 ± 4.2	46.0 ± 5.5	0.495	0.021
IVSTd (mm)	14.1 ± 1.9	13.4 ± 2.1	12.5 ± 1.4	0.007	14.2 ± 1.9	14.2 ± 1.6	14.2 ± 1.9	0.815	0.032
LVIDd (mm)	46.5 ± 5.4	47.7 ± 4.7	47.3 ± 6.0	0.232	44.5 ± 8.5	45.3 ± 6.8	46.4 ± 7.6	0.417	0.097
PWTd (mm)	11.1 ± 2.7	9.9 ± 3.3	9.3 ± 2.8	<0.001	12.0 ± 3.4	11.7 ± 2.1	11.3 ± 3.0	0.676	0.019
LV end-diastolic volume (ml)	87.0 ± 28.5	87.1 ± 28.7	84.6 ± 45.4	0.635	85.9 ± 36.5	86.0 ± 40.7	84.0 ± 37.8	0.966	0.783
LV end-systolic volume (ml)	32.8 ± 16.1	27.7 ± 13.5	25.6 ± 12.5	<0.001	31.1 ± 18.2	30.6 ± 16.1	31.8 ± 19.5	0.811	0.015
LVEF Simpson (%)	63.1 ± 8.1	69.1 ± 7.5	70.1 ± 11.5	<0.001	64.3 ± 7.2	63.9 ± 8.9	62.9 ± 8.1	0.467	0.048
LV mass/body surface area (g/m^2)	112.4 ± 33.9	103.6 ± 30.5	94.9 ± 29.8	0.004	114.8 ± 41.6	115.3 ± 23.3	118.7 ± 30.1	0.634	0.004
LV mass/height$^{2.7}$ ($g/m^{2.7}$)	53.9 ± 15.6	47.0 ± 14.2	44.7 ± 14.9	<0.001	55.7 ± 15.3	55.8 ± 17.4	58.6 ± 16.1	0.369	<0.001
Mitral valve E Vmax (cm/s)	74.2 ± 21.0	70.3 ± 17.0	74.3 ± 24.4	0.708	74.7 ± 31.4	74.2 ± 26.4	76.5 ± 22.5	0.892	0.987
Mitral valve A Vmax (cm/s)	85.8 ± 23.7	79.7 ± 17.6	79.6 ± 21.7	0.028	78.6 ± 50.9	83.6 ± 27.6	85.6 ± 28.8	0.609	0.048
Mitral valve E/A ratio	0.89 ± 0.29	0.90 ± 0.27	1.12 ± 0.88	0.183	0.88 ± 0.21	0.87 ± 0.25	0.90 ± 0.25	0.878	0.387
Mitral valve E deceleration time (ms)	227.2 ± 66.5	211.3 ± 57.6	185.2 ± 67.1	0.003	236.0 ± 115.0	253.9 ± 70.4	233.4 ± 89.0	0.745	0.008
Mitral valve lateral E' (cm/s)	8.1 ± 2.8	9.5 ± 2.4	9.9 ± 2.7	0.001	6.6 ± 2.5	6.1 ± 2.5	6.3 ± 1.7	0.541	0.023
Mitral valve lateral E/E'	9.9 ± 4.0	7.9 ± 2.2	7.4 ± 2.7	<0.001	10.9 ± 3.0	12.3 ± 4.2	12.1 ± 3.8	0.495	0.001
Isovolumic relaxation time (ms)	109.1 ± 21.7	93.0 ± 22.4	85.6 ± 24,4	0.002	119.4 ± 26.3	111.8 ± 14.0	111.6 ± 40.7	0.615	<0.001
TAPSE (mm)	22.8 ± 6.1	24.9 ± 5.8	25.75 ± 6.8	0.009	21.9 ± 8.9	22.6 ± 11.9	22.2 ± 7.6	0.949	0.063
Laboratory tests									
Serum creatinine (mg/dl)	0.98 ± 0.3	1.01 ± 0.4	0.93 ± 0.7	0.519	0.98 ± 0.50	0.99 ± 0.63	0.90 ± 0.51	0.741	0.891
eGFR (ml/min/1.73 m^2)	83.5 ± 27.8	80.1 ± 28.5	84.7 ± 31.2	0.592	80.5 ± 29.3	80.9 ± 36.5	89.5 ± 28.8	0.343	0.476
NT-pro-BNP (ng/l)	760 ± 1,451	564 ± 1,072	492 ± 1,078	0.274	1,115 ± 1,700	1,101 ± 1,491	1,022 ± 1,798	0.876	0.583

Values are mean ± SD. Differential efficacy between RD and control group was tested using the group square linear trend interaction test.

DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; IVSTd = end-diastolic interventricular septum thickness; LVEF = left ventricular ejection fraction; LVIDd = end-diastolic left ventricular internal dimension; PP = pulse pressure; PWTd = left ventricular end-diastolic posterior wall thickness; SBP = systolic blood pressure; TAPSE = systolic lateral tricuspid annulus excursion.

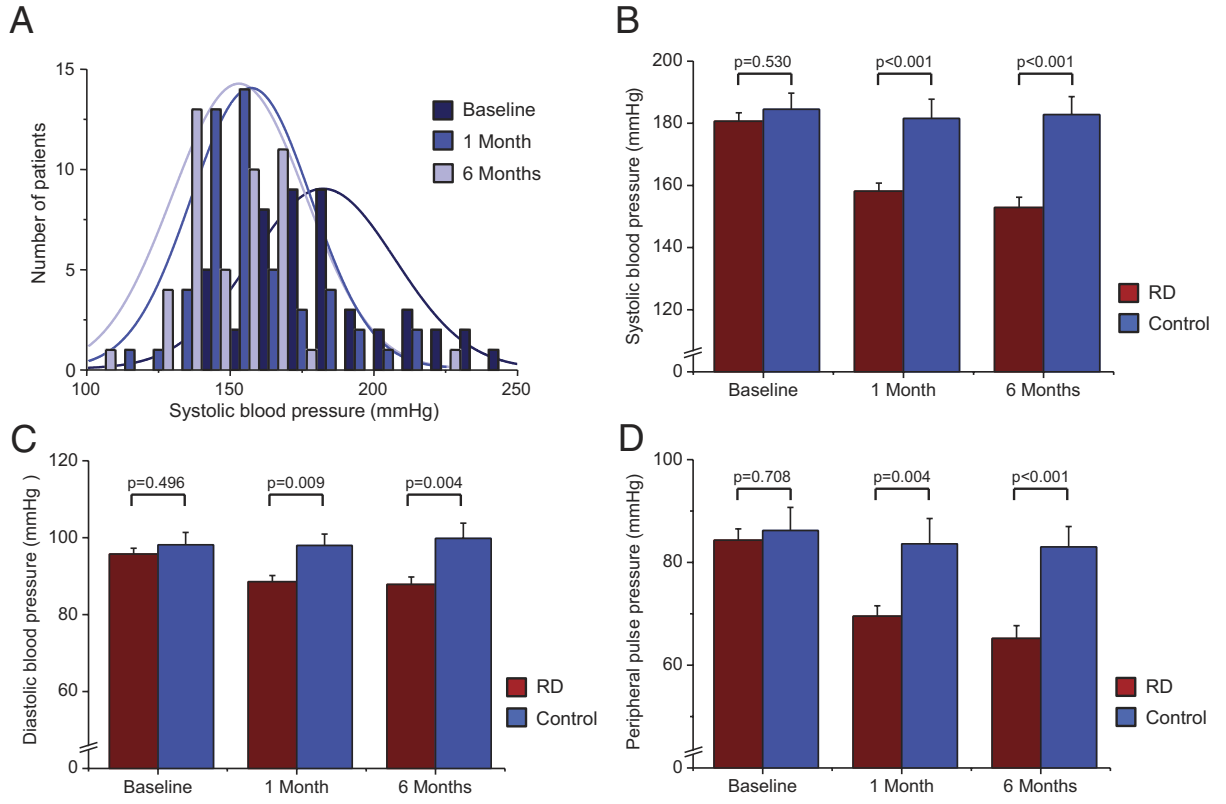

Figure 1 **Effect of RD on BP and Pulse Pressure in Patients With Resistant Hypertension**

(A) Distribution of systolic blood pressure (SBP) in the renal sympathetic denervation (RD) group at baseline **(dark blue)** and after 1 month **(medium blue)** and 6 months **(light blue)**. **(B)** Systolic blood pressure, **(C)** diastolic blood pressure (DBP), and **(D)** pulse pressure in patients who underwent RD **(black)** and in control patients **(white)** at baseline, 1 month, and 6 months. p Values RD versus control are indicated above the columns. In the treatment group, p for statistical trend was $p < 0.001$ for SBP **(B)**, $p < 0.001$ for DBP **(C)**, and $p < 0.001$ for pulse pressure **(D)**. Values are presented as mean ± standard error.

≥12) declined from 29% at baseline to 4% after 1 month and 6 months, respectively (16).

A decrease of the E/E' ratio after RD, indicating reduction of LV filling pressures, was particularly pronounced in patients with elevated baseline values above the median of 8.8. In this subgroup, E/E′ decreased by −4.2 ± 2.9 at 1 month ($p < 0.001$) and −4.4 ± 3.1 at 6 months ($p = 0.013$) post-RD (Fig. 3B). Moreover, reduction of the E/E′ ratio was more marked in the presence of LVH. Although in patients without LVH (indexed to height$^{2.7}$), no significant change of the E/E′ ratio 6 months after RD occurred (−0.17 ± 1.7; $p = 0.42$ vs. baseline), in the subgroup with LVH at baseline, RD reduced the E/E′ ratio by −3.0 ± 3.2 ($p = 0.032$ vs. no LVH, $p = 0.012$ vs. baseline).

Consistent with a pronounced reduction in LV filling pressures by RD, left atrial (LA) size significantly decreased after RD, whereas in the control group, LA size significantly increased during follow-up (Table 2). At baseline, 55% in the RD group and 45% in the control group had increased LA diameters >44 mm. This percentage declined to 35% 6 months after RD, whereas in control patients, the percentage remained statistically unchanged at 46%.

RD-induced LVH regression not exclusively associated with BP reduction. To evaluate a potential impact of the efficacy of BP reduction by RD on regression of LVH and improvement of diastolic function, patients were divided into tertiles according to the SBP decrease after 1 month and 6 months, respectively. As demonstrated in Figure 4, both regression of LV mass and reduction of the E/E′ ratio were most pronounced in patients with the most marked SBP decrease.

Six patients (13%) showed <10 mm Hg BP-lowering response 6 months after RD, previously defined as "nonresponders" (12). Notably, in 5 of these patients, we still obtained a marked reduction of the LV mass index by −8.8 ± 6.6 g/m$^{2.7}$ and in 4 patients a decrease of the E/E′ ratio by −4.9 ± 5.2, indicating BP-independent effects of RD on LVH and diastolic dysfunction.

Discussion

Although for many years, reduction of peripheral BP per se was the target in the treatment of patients with arterial hypertension, increasing evidence indicates that the mode of

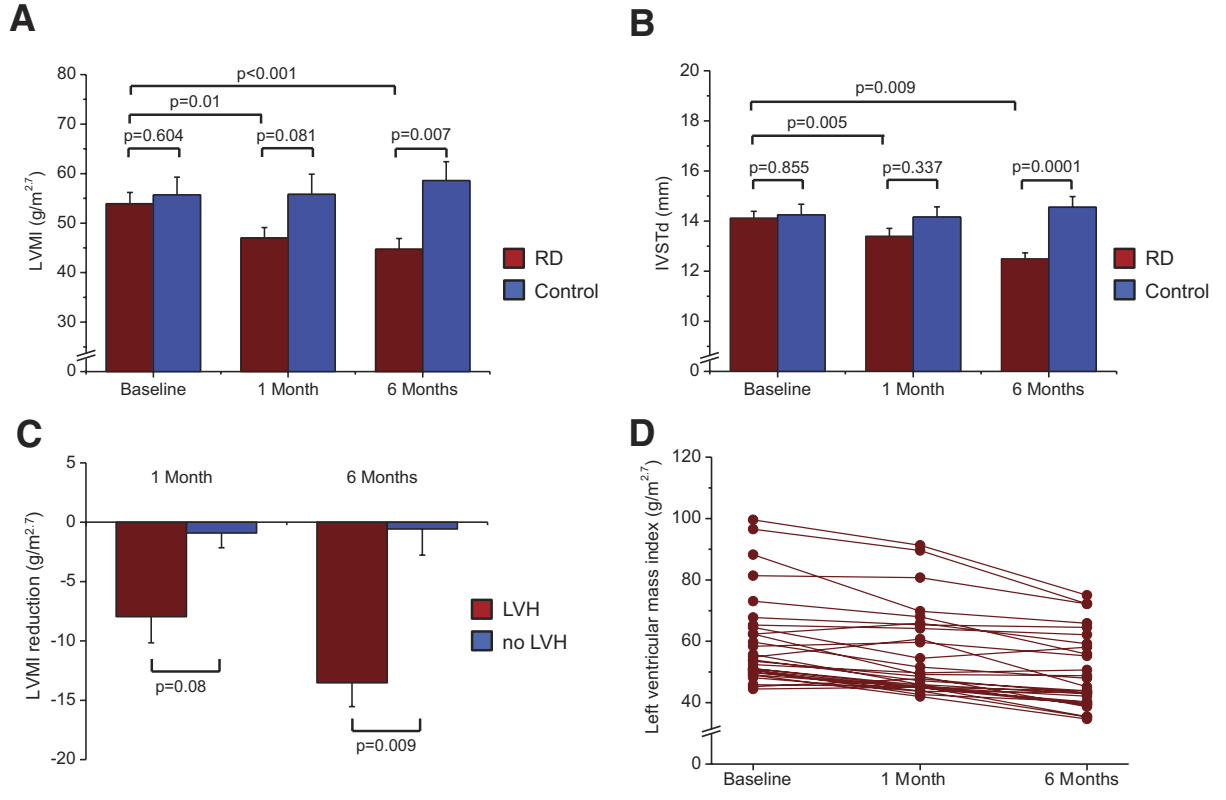

Figure 2 **Impact of RD on LV Mass**

(A) Left ventricular (LV) mass/height$^{2.7}$ and **(B)** end-diastolic interventricular septum thickness (IVSTd) measured in renal sympathetic denervation (RD) and control patients at baseline, 1 month, and 6 months. While there was a steady decrease in the average left ventricular (LV) mass and IVSTd after RD, these parameters slightly increased in control patients. In the treatment group, p for statistical trend was p = 0.004 for LV mass/height$^{2.7}$ **(A)**, p = 0.007 for IVSTd **(B)**. **(C)** Differential effect of RD on LV mass regression depends on the degree of left ventricular hypertrophy (LVH) at baseline. LV mass/height$^{2.7}$ regression by RD was significantly greater in those patients with LVH at baseline. Values are presented as mean ± standard error. **(D)** Regression of LV mass after RD in individual patients with a LVH at baseline (n = 29). LVMI = left ventricular mass index.

BP control may differentially affect outcome (20,21). Critically, it has been discussed that the lowering of peripheral BP rather represents a surrogate endpoint that does not automatically lead to a parallel decrease in cardiovascular morbidity and mortality (7). Conversely, intermediate endpoints such as LVH were shown to be reliably linked to cardiovascular prognosis (22,23). LVH is an indicator of end-organ damage in arterial hypertension. The presence of LVH is associated with an increased rate of cardiovascular events and death independent of other cardiovascular risk factors and, notably, independent of BP values (5,24,27). Consistently, LVH regression was accompanied by favorable outcome (22,23). In this respect, it is of importance that in the present study, in addition to the BP-lowering effect, we were able to demonstrate early and marked reduction of LV mass and improvement of diastolic dysfunction by RD in patients with therapy-resistant hypertension.

Chronic activation of the sympathetic nervous system is involved in the development and maintenance of arterial hypertension (9,28). Moreover, sympathetic overactivity is a key component of the signaling pathways altered in hypertension-related cardiac remodeling (10,11). However, in the LIFE (Losartan Intervention For Endpoint reduction in Hypertension) study, antihypertensive treatment with atenolol-based therapy resulted in less LVH regression than a losartan-based strategy (29). This clinical observation was further supported by a meta-analysis demonstrating that beta-blockers induced significantly less LVH regression compared with various other antihypertensive drugs, especially blockers of the rennin-angiotensin system (8). The diminished efficacy of beta-blockers on LVH reduction might reside in their inability to decrease myocardial fibrosis (30). Experimental evidence indicates that the sympathetic nervous system mediates hypertension-induced hypertrophy via direct stimulation of cardiomyocyte beta-adrenergic receptors (31). Conversely, cardiac fibrosis and inflammation have been suggested to result from a self-perpetuating circuit involving mast cell activation, stimulation of afferent sympathetic nerves, angiotensin II production, and norepinephrine release, rather than being mediated via alpha-adrenergic receptors (32). In line with this notion, in a hypertensive rat model, both beta-blockade and sympathec-

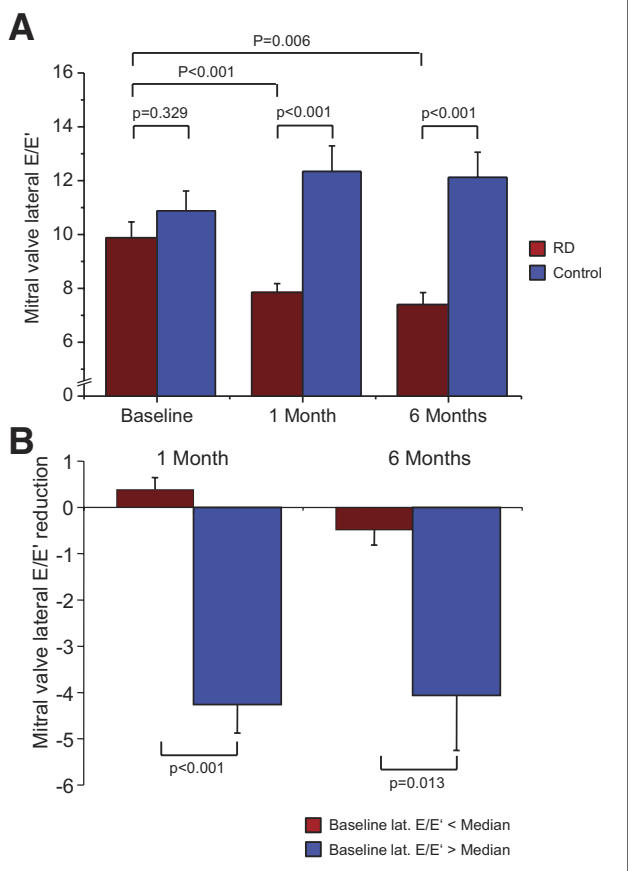

Figure 3 **Effect of RD on Diastolic Function**

(A) Mitral valve lateral (lat.) E/E′ at baseline, 1 month, and 6 months in renal sympathetic denervation (RD) and control patients. While no significant changes could be detected in the control group, E/E′ significantly decreased in the RD group. In the treatment group, p for trend was <0.001. **(B)** Differential effect of RD on E/E′ reduction depended on the degree of diastolic dysfunction at baseline. Reduction of E/E′ by RD was significantly greater in those patients with an E/E′ above the median of 8.8 at baseline. Values are presented as mean ± standard error.

tomy attenuated LVH, whereas accompanying myocardial interstitial fibrosis was abolished by sympathectomy or doxazosin but left unchanged by beta-blockade (31). These effects were independent of BP control (31).

Catheter-based RD reduces renal sympathetic efferent activity shown by a reduction of noradrenaline spillover (33). Furthermore, whole-body sympathetic activation is reduced by the ablation of afferent renal nerves, which stimulate sympathetic outflow in the hypothalamus (9,34). Thus, in contrast to beta-blockers, RD will diminish both beta- and alpha-receptor–mediated hyperactivity. In the present study, we obtained a pronounced reduction of LV mass by 9.2 g/m$^{2.7}$ (−17% from baseline) after RD, indicating a more pronounced effect of RD in this treatment-resistant patient group compared with drug interventions for uncomplicated hypertension (35). Although it is not possible to distinguish how much of these changes were caused by BP reduction related to RD versus sympathetic denervation per se, consistent with animal models, LV mass regression occurred also in 5 of 6 RD "nonresponders" (12), supporting the notion of BP-independent effects of RD on LVH. Besides the aforementioned signaling pathways, these antihypertrophic effects might in part be mediated via reduced insulin concentrations after RD (14).

Both concentric and asymmetric myocardial hypertrophy are indicators of adverse prognosis (36). IVSTd was increased in all our patients, with a majority presenting concentric LVH (RWT >0.42) similar to previous reports (37,38). In these patients, we consistently observed regression of IVSTd and LV mass. However, we are not able to evaluate the impact of RD on eccentric hypertrophy, that is, RWT ≤0.42, because of the limited number of patients with this LV geometry in our population (15,19).

Several studies indicated a close relation between refractory hypertension and LVH, as well as LVH and diastolic dysfunction (39,40). However, abnormalities of diastolic function have also been found in patients without measur-

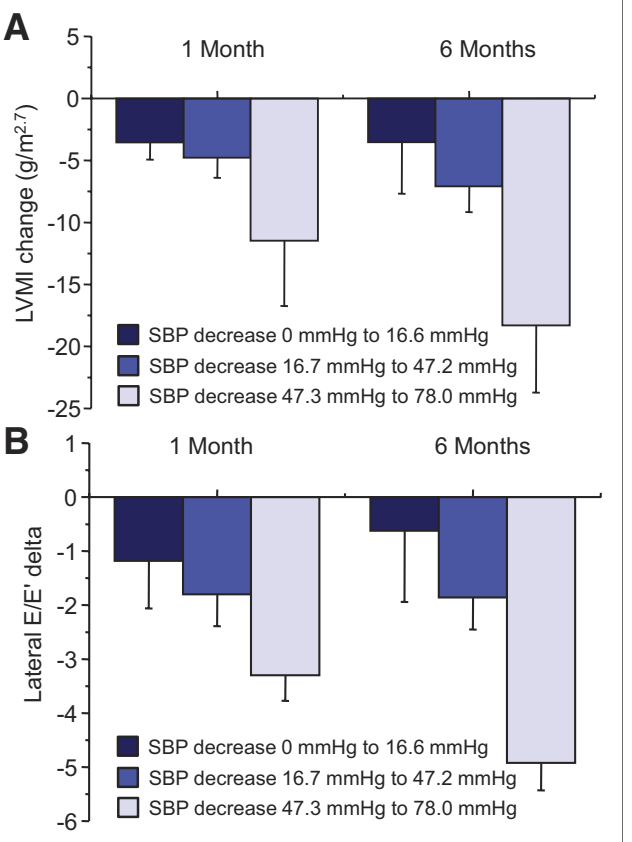

Figure 4 **Regression of LVH and Improvement of Diastolic Function Depending on BP Reduction Achieved by RD**

Patients were divided into tertiles according to the SBP decrease after 1 month and 6 months, respectively. Both regression of LV mass/height$^{2.7}$ **(A)** and reduction of the E/E′ ratio **(B)** were most pronounced in patients with the most marked SBP decrease. Values are presented as mean ± standard error. Abbreviations as in Figures 1 and 2.

able myocardial hypertrophy (2,3). In the present study, besides inducing LVH regression, RD significantly improved cardiac functional parameters. Renal sympathetic nerve ablation reduced LV volumes, increased the ejection fraction, and improved diastolic dysfunction, such as myocardial relaxation and end-diastolic pressures as indicated by left ventricular mitral valve E/E′ and LA size, which have been linked to improved prognosis in pharmaceutical interventional trials (22,23). Diastolic function is modulated by multiple factors. Reduction of LV filling pressure and regression of LV wall thickness will have improved diastolic dysfunction after RD. A potential impact of RD on myocardial fibrosis remains speculative. Although pressure overload per se affects myocardial collagen content, reduction of sympathetic and renin-angiotensin-aldosterone system activity, known to occur after RD, might also facilitate regression of myocardial fibrosis (41).

Study limitations. Given the lack of other therapeutic options for resistant arterial hypertension, we are not able to compare the effects of RD with other treatment strategies. The cohort in our study was comparatively small with a follow-up of 6 months, not allowing analysis of clinical outcome. Future results of this trial with longer follow-up and a larger cohort of treated patients will therefore be of interest.

Conclusions

RD offers a novel and safe catheter-based approach for selective reduction of renal sympathetic drive. We demonstrate for the first time to our knowledge that selective denervation of the renal sympathetic nerves in addition to lowering peripheral BP significantly reduces LV mass and improves diastolic function in patients with resistant hypertension. Extrapolating from drug trials (22,23), the effect on cardiac remodeling documented in our study suggests a prognostic benefit of RD in patients with refractory hypertension, which should be evaluated in future trials.

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Key Words: diastolic function ■ hypertrophy ■ myocardial mass ■ renal denervation ■ resistant hypertension.